Please add claim 18 as follows:

18. The mutant *C. fetus* strain of claim 1, wherein all but one of the *sapA* homologs are altered due to the insertion of said DNA cassette.

Please cancel claim 3.

REMARKS

Priority

Claims reciting HIV were not afforded the filing date as the provisional application. Applicants submit that the provisional application filed January 31, 1997 did have disclosure on HIV (Example 12). Accordingly, Applicants respectfully request that claims which recite HIV be afforded the earliest filing date.

Drawings

Table 1 was cut off on page 18. Applicants submit a replacement sheet for page 18 that shows a complete Table 1.

Sequence Compliance

Sequences were recited in the specification but no SEQ ID No. was provided. The specification has been amended with assignment of SEQ ID Numbers.

Incorporation by reference of essential material

The Examiner cited improper incorporation of essential material. However, the Examiner did not state what and where is the incorporation deemed improper by the Examiner. Accordingly, Applicants do not have information to respond to this issue.

Specification

The specification has been amended to reflect the foreign priority entitled to this application.

The 35 U.S.C. §101 Rejection

Claims 1, 2, 3, 7 stand rejected under 35 U.S.C. §101 as directed to non-statutory subject matter. The rejection is respectfully traversed.

The Examiner argued that the prior art teaches that the bacteria "possess multiple partially homologous, and therefore encode heterologous, antigens". Applicants respectfully disagree. The *Campylobacter fetus* bacteria have 7-9 highly homologous gene cassettes encoding different *sapA* homologs. As it is readily understood by one of ordinary skill in the art, these *sapA* homologs are homologous, not heterologous, proteins with respect to the bacteria that expresses the proteins. In contrast, the mutant strain

of the present invention contains a DNA cassette that encodes a heterologous protein, i.e. a foreign protein with respect to the mutant strain. Examples of inserted heterologous proteins include immunogens from *Salmonella*, *Shigella*, *Campylobacter jejuni*, *E. coli* 0157:H7, human immunodeficiency virus, simian immunodeficiency virus and other animal pathogens. Hence, the claimed mutant strain does not occur in nature. Claim 1 has been amended to recite a non-naturally occurring mutant *C. fetus* strain. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 3, 7 under 35 U.S.C. §101 be withdrawn.

The 35 U.S.C. §112 Rejection

Claims 1-17 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is traversed.

Applicants respectfully submit that the claim mutant may be obtained by a repeatable method that is described fully by the specification. Indeed, the method of obtaining the mutant strain is described in Examples 4 and 9 and the reagents required are known to those having ordinary skill in this art as described by Example 4. Applicants respectfully request that the rejection of claims 1-17 under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 2, 4, 5, 8 and 14 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

Claim 2 has been amended to recite the insertion of the DNA cassette results in alteration of a *sapA* homolog. Claim 4 has been amended to recite the expression of the DNA cassette results in a S-layer protein chimera. Claim 5 has been amended to recite the DNA cassette encodes immunogens of a pathogen, wherein said pathogen is selected from the Markush group of pathogens.

Claim 8 recites a Markush group containing an antigen and a therapeutic agent. Applicants submit that claim 1 from which claim 8 depends only recites a heterologous protein, not an antigen as argued by the Examiner. Hence, claim 8 further limits the heterologous protein in claim 1 to an antigen or a therapeutic agent. Claim 14 recites sapCDEF gene, and the sequence for the gene was published in Thompson SA, Shedd OL, Ray KC, Jorgensen JP, Blaser MJ, *Campylobacter fetus surface layer proteins are transported by a Type I secretion system.*, J. Bacteriol 1998: 180: 6450-8. Accordingly, Applicants submit that the rejection of claims 2, 4, 5, 8 and 14 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 1-4 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Fujita** et al. The rejection is traversed.

Fujita et al. teach the typing of naturally occurring strains by Southern blotting. **Fujita** et al. did not teach any mutant strain as claimed in the present application. **Fujita** et al. did not teach "isolated mutant strains was identified through the lack of hybridization of a conserved sequence of sapA with the strains" as argued by the Examiner. The lack of hybridization was due the lack of type A LPS production in type B and type NANB strains (page 445, first paragraph of Results and discussion). These are not mutants. Furthermore, **Fujita** et al. did not teach any non-naturally occurring mutant strain that expresses a heterologous (i.e. foreign) protein as claimed in the present invention. Hence, the present invention is distinct and different from **Fujita** et al. Accordingly, Applicants respectfully submit that the rejection of claims 1-4 under 35 U.S.C. §102(b) be withdrawn.

Claims 1-3, 6-8 stand rejected under 35 U.S.C. §102(a) as being anticipated by **Dworkin** et al (March 1996). The rejection is respectfully traversed.

Dworkin et al. discloses that the sapA gene expression relies on a single promoter which is switched among the eight genomic SLP gene cassettes by reciprocal recombination. **Dworkin** et al. did not teach or suggest making and using mutant strain that expresses foreign heterologous protein for vaccination purpose as claimed in the present invention. Hence, the prior art did not anticipate the present invention. Accordingly, Applicants respectfully submit that the rejection of claims 1-3, 6-8 under 35 U.S.C. §102(a) be withdrawn.

Claims 14-16 were rejected under 35 U.S.C. §102(b) as being anticipated by **Dworkin** et al. (June 1995). The rejection is respectfully traversed.

Dworkin et al. teach the cloning of *sapB* gene. In contrast, claim 14 is drawn to a bacteria strain modified to express the *sapCDEF* gene. These two genes are totally different and distinct from each other. *sapB* gene encodes a surface protein that is involved in antigenic variation of *C. fetus*, whereas *sapCDEF* encodes a transporter involved in the translocation of protein across the bacterial envelopes (Example 14). **Dworkin** et al. did not teach or suggest modifying a bacteria to express the *sapCDEF* gene. Hence, the present invention is distinct and different from **Dworkin** et al..

Accordingly, Applicants respectfully submit that the rejection of claims 14-16 under 35 U.S.C. §102(b) be withdrawn.

Claims 1-4, 6-8 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Blaser** (November 1994 or November 1993). The rejection is respectfully traversed.

Blaser et al. describes the insertion of a kanamycin cassette into sapA as a selective marker to study S-layer protein allele switching. However, **Blaser** et al. did not teach or suggest using the mutant strains for vaccination purposes. Hence, the cited **Blaser** et al. references do not anticipate the present invention. Accordingly, Applicants respectfully submit that the rejection of claims 1-4, 6-8 under 35 U.S.C. §102(b) be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 14 and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Blaser** (1993) in view of **Dworkin** et al (1995). The rejection is respectfully traversed.

Blaser teaches the structure and function of sapA homologs in serum resistance and antigenic variation of *C. fetus*. **Dworkin** et al (April 1995) teach cloning of a sapA homolog in *E. coli*. Neither reference teach or suggest making and using a bacteria

modified to express *sapCDEF* gene, nor do these references teach or suggest using such modified bacteria to immunize a host to generate immune response.

The Examiner argued that it is obvious to "modify the invention of **Blaser** in view of the teachings of **Dworkin** and immunize a host with a bacteria modified with *sapCDEF* gene because **Dworkin** teaches the successful cloning of *C. fetus* sap gene". Applicants strongly disagree. First of all, there is no teaching or suggestion in the either of the cited references on either immunizing a host with modified bacteria, or bacteria modified with *sapCDEF* gene. Secondly, there is no teaching or suggestion in the either of the references on the *sapCDEF* gene. The cited references only teach the homologs of sap gene, which is not the subject matter in claims 14 and 17. Homologs of sap gene encode surface proteins that are involved in antigenic variation of *C. fetus* as taught in **Blaser**, whereas *sapCDEF* encodes a transporter involved in the translocation of protein across bacterial envelopes (present invention, Example 14). Hence, *sapCDEF* gene is totally different and distinct from the homologs of sap gene. The cited prior art do not teach or suggest using bacteria modified with *sapCDEF* gene to immunize a host to generate immune responses.

The Examiner argued that one of skill in the art "would have been motivated to obtain an immune response to the modified bacteria which contains the *sapCDEF* gene because ..... S-protein layers are a critical virulence factor". Applicants strongly disagree. The gene product of *sapCDEF* gene has a function different from that of S-layer proteins as discussed above. The cited prior art do not teach or suggest using *sapCDEF* gene. It is illogical for one of skill in the art to be motivated in view of the teaching on sap homologs to obtain an immune response using bacteria modified with a gene, the *sapCDEF* gene, which is unrelated to the sap homologs and has no significant role in the virulence of the bacteria.

The Examiner further argued that "**Blaser** suggests the construction and use of modified bacteria to obtain antibodies to use in an animal model that provides insight into disease processes". Applicants strongly disagree. **Blaser** did not teach or suggest making and using of modified bacteria for studies in animal model, nor did he teach or suggest making and using modified bacteria in immunization as claimed herein.

In the absence of any other teaching, Applicants submit that the Examiner has failed to demonstrate any prior art teaching that establishes the *prima facie* obviousness of claims reciting a

bacteria modified to express *sapCDEF* gene and a method of using such bacteria to immunize a host. Because of this failure to show some objective teaching in the prior art, there has been a failure to establish a *prima facie* case of obviousness. As none of the references suggest or teach the current invention, it would appear that the Examiner has used hindsight wherein what the inventor taught is used against the teacher. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 21 F.2d 1540, 553 (Fed. Cir. 1993). Since none of the cited references, individually or in combination, teach the features recited in claims 14 and 17, Applicants assert that the Examiner has failed to provide a *prima facie* case of obviousness and accordingly, request that this rejection be withdrawn.

Claims 1-8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Blaser** (1994) in view of **Lubitz** et al. The rejection is respectfully traversed.

Blaser et al. describes the insertion of a kanamycin cassette into sapA as a selective marker to study S-layer protein allele switching. However, **Blaser** et al. did not teach or suggest using the mutant strains for vaccination purposes. **Lubitz** et al. teach the making and use of bacterial ghosts to carry immunogens by first expressing a fusion protein that inserts into the bacterial

membrane, and then express a lytic gene that lyses the bacteria. The invention of **Lubitz** et al. does not involve modification of sap homologs in *C. fetus* as claimed herein. Hence, **Lubitz** et al. is actually teaching away from the present invention. Thus, combining the teaching of **Blaser** that did not teach or suggest using modified bacteria for vaccination with the teaching of **Lubitz** that did not teach or suggest modification involving sap homologs would not result in the present invention of using modified *C. fetus* expressing altered sap homologs for vaccinating an animal.

In view of the above remarks, the combined teaching of the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed invention. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully submit that the rejection of claims 1-8 under 35 U.S.C. §103(a) be withdrawn.

Claims 1-8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Blaser** (1994) in view of **Szostak** et al (1996). The rejection is respectfully traversed.

Blaser et al. describes the insertion of a kanamycin cassette into sapA as a selective marker to study S-layer protein allele switching. However, **Blaser** et al. did not teach or suggest using the mutant strains for vaccination purposes. **Szostak** et al teach the making of bacterial ghosts by controlled expression of a bacteriophage lysis gene and using such bacterial ghosts as non-living candidate vaccines. The invention of **Szostak** et al. does not involve modification of sap homologs in *C. fetus* as claimed herein. Hence, **Szostak** et al. is teaching away from the present invention.

The Examiner argued that "**Szostak** et al. is cited to show the use of S-layer proteins as a vehicle of foreign antigen presentation". Applicants strongly disagree. **Szostak** et al. did not teach or suggest anything about S-layer proteins, nor did **Szostak** et al. show the use of S-layer proteins as a vehicle of foreign antigen presentation. Furthermore, the Examiner did not state how the two references could be combined to produce the present invention. Applicants assert that combining the teaching of **Blaser** that did not teach or suggest using modified bacteria for vaccination with the teaching of **Szostak** that did not teach or suggest modification involving sap homologs would not result in the present invention of

using modified *C. fetus* expressing altered sap homologs for vaccination purposes.

In view of the above remarks, the combined teaching of the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed invention. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants request that the rejection of claims 1-8 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed April 27, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: July 31, 2000

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